Risk compensation and STI incidence in PrEP programmes: Latest evidence and research gaps

Matthew Quaife, Louis MacGregor, Jason J Ong, Mitzy Gafos, Sergio Torres-Rueda, Hannah Grant, Peter Vickerman

Department of Global Health and Development, London School of Hygiene and Tropical Medicine, London, UK (Matthew Quaife PhD, Mitzy Gafos PhD, Sergio Torres-Rueda MSc, Hannah Grant MSc).

Population Health Sciences, University of Bristol, Bristol, UK (Louis MacGregor MSc, Prof Peter Vickerman DPhil)

Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK (Jason Ong PhD)

Central Clinical School, Monash University, Melbourne, Australia (Jason Ong PhD)

Corresponding author: Matthew Quaife. matthew.quaife@lshtm.ac.uk

Pre-exposure prophylaxis (PrEP) for HIV prevention is recommended by the WHO as part of a comprehensive HIV prevention package for those at substantial risk of HIV infection[1]. PrEP is effective at preventing HIV acquisition, demonstrated by high efficacy in placebo-controlled trials and demonstration projects, and increased PrEP coverage is associated with substantial decreases in population-level HIV incidence among men who have sex with men (MSM) in high-income settings[2-4]. Although PrEP is effective in preventing HIV infection, reduced condom use or other increases in sexual risk taking risk may increase STI transmission, especially in populations with low PrEP adherence, an increase in STIs may play an important role in affecting HIV transmission dynamics.

Before PrEP was widely available, some urged caution in recommending it because of the potential for *risk compensation*. As cyclists ride faster when made to wear helmets[5], so might PrEP users increase condomless sex or sexual partners, increasing the risk of other sexually transmitted infections (STIs)[6, 7]. As defined elsewhere[1], risk compensation refers to an increase in risk-related behaviours, because an intervention reduces perceptions of risk among individuals or a population.

Self-reported condom use and STIs did not change in placebo-controlled PrEP studies[3, 8]. However, in some open-label studies where users knew they were taking highly effective PrEP, PrEP use was associated with increases in condomless sex and, most importantly, STIs[9]. One observational study showed evidence of community-level risk compensation, where MSM *not* using PrEP also reduced condom use as PrEP coverage increased[10]. Importantly, six presentations at the 22nd International AIDS Conference in Amsterdam (Table 1) provide further evidence of risk compensation.

HIV prevention is at a crossroads.. The potential effects of increasing STI incidence must be understood alongside the HIV benefits of PrEP, especially with suboptimal adherence or antibiotic-resistant STIs. We make an urgent call for more evidence on the potential effect of individual and community-level risk compensation on HIV and STI transmission among all groups where PrEP is available, alongside proportionate and context-specific programming and communication to mitigate risk compensation.

First, we do not understand how PrEP will affect epidemic dynamics well enough to make informed trade-offs between disease burdens from HIV and STIs. Models have not always predicted HIV epidemics accurately to-date[11], and more data are needed to fully understand the long-term impact of PrEP in a variety of real-world settings, in order to improve incorrect assumptions which reduce our confidence in their projections. Yet modelling is an important component of the health technology appraisal process, and will be critical to understand how PrEP's impact is affected by risk compensation

and resulting changes in STI dynamics[12]. There are currently few behavioural data to parameterise PrEP models, for example risk compensation may cluster among people with different risk factors (e.g. multiple partners or seroconcordance) which are not accurately reflected in sexual mixing assumptions. PrEP guidelines also require regular STI testing which could increase early diagnosis and treatment, potentially counteracting or even surpassing the effect of any increases in risky sexual behaviour.**Second, the majority of evidence on risk compensation exists among MSM groups in high-income countries**. Yet PrEP is now a key part of HIV prevention programmes among other high-risk groups, for example adolescent girls and young women in sub-Saharan Africa. We have little evidence on risk compensation or PrEP adherence among these groups. The burden of STI acquisition is also much higher among women of reproductive age, where chlamydia and gonorrhoea can cause a range of reproductive morbidity and display increasing antibiotic resistance. Therefore, the generalisability of risk compensation evidence and its implications outside high-income MSM groups is very limited.

Third, more evidence is needed on the effect of community-level risk compensation; in particular sexual behaviours among non-PrEP users in the context of PrEP availability, and early treatment for people living with HIV (PLHIV). Risk compensation is unlikely to undermine the HIV prevention benefits of PrEP among adherent PrEP users. However, small behavioural changes among non-users may reduce PrEP's overall epidemiological benefit. To model this, it is important to quantify the extent to which PLHIV are likely to have undetectable viral loads and/or STIs, particularly in low and middle-income countries where data is scarce.

Fourth, more research is needed on how users understand PrEP as a complement or substitute for alternate prevention strategies. Although guidelines recommend that PrEP users be counselled to use condoms, these are inconsistent since eligibility criteria for PrEP include reporting inconsistent condom use. Different, effective alternatives may therefore be needed to prevent STIs alongside PrEP, as condoms may be hard to promote among people who are primarily concerned with HIV prevention. The extent to which PrEP is used as a substitute to condoms, is likely to vary between populations and contexts. It is critical that we understand behavioural and structural approaches that support the provision of combination prevention services and tailored prevention packages.

Finally, where intermittent PrEP is provided, evidence is needed to understand behaviours before, during, and between episodes of use. Since intermittent PrEP regimens depend partly on user risk perception, it is important to understand how the choice to use PrEP is made, and how time on PrEP impacts risk behaviours surrounding episodes of PrEP use. Importantly, risk perceptions are rarely measured but inferred from behaviour change without knowing why behaviours changed – more work on measuring risk changing risk perceptions is needed.

PrEP has an important role in HIV prevention, and uncertainty in its effect on risk compensation and STI incidence should not prevent provision to those at high risk. Nonetheless, in order to support effective PrEP programming, researchers and practitioners need reliable and robust behavioural evidence from all populations to evaluate its true risks and benefits.

Declaration of interest statement: No interests to declare

Authors	Title	Study Population, Location	Evidence type	Findings related to risk compensation
Rendina et al. http://programme.aids2018.org/Abstract/Abstract/8121	Changes in rectal STI incidence and behavioral HIV risk before, during, and after PrEP in a national sample of gay and bisexual men in the United States	MSM, multiple sites, United States of America	Behavioural indicators, STI incidence	• No change in odds of rectal STI during PrEP use or after discontinuation compared to before uptake • Compared to before PrEP use: ○ 156% increase in condomless anal sex with casual partners ○ 410% increase in receptive condomless anal sex with serodiscordant male partners while on PrEP, but average of <1 act per person
De Wit et al. http://programme.aids2018.org/Abstract/Abstract/10801	Attitudes regarding HIV, PrEP and condom use jointly predict risk compensation among men who have sex with men - findings from the VicPrEP implementation project, Melbourne	MSM, Melbourne, Australia	Behavioural indicators	• Frequency of condom use for anal sex with causal partners decreased significantly over one year follow up • Median condom protected acts in last three months reduced from 3 to 2
Traeger et al. http://programme.aids2018.org/Abstract/Abstract/3905	Changes, patterns and predictors of sexually transmitted infections in gay and bisexual men using PrEP; interim analysis from the PrEPX demonstration study	MSM, Melbourne, Australia	Behavioural indicators, STI incidence	• STI incidence (chlamydia, gonorrhea, syphilis, and rectal pharyngeal or urethral infections) increased after PrEP use compared to before (IRR: 1.42 95%CI: 1.29-1.56)
Molina et al. http://programme.aids2018.org/Abstract/Abstract/13278	Incidence of HIV-infection in the ANRS Prevenir Study in the Paris Region with Daily or On Demand PrEP with TDF/FTC	MSM, Paris, France	Behavioural indicators	• Indicative (not statistically tested) evidence of behavioural risk compensation (condomless sex at last intercourse, number of condomless acts in previous 4 weeks)
Prestage et al. http://programme.aids2018.org/	A longitudinal analysis of the impact of PrEP on sexual	MSM, multiple	Behavioural indicators	• Among PrEP users significant increase in: ○ Condomless anal sex (78% increase)

Abstract/Abstract/8042	behaviour and drug use among Australian gay and bisexual men	sites, Australia		○ number of partners in previous six months (100% increase) ○ Proportion reporting group sex (96% increase)
Morris et al. http://programme.aids2018.org/ Abstract/Abstract/11478	High HIV PrEP adherence is associated with syphilis incidence	MSM, California, United States of America		• The incidence rate of syphilis was over 3 times higher among those highly adherent (≥1246 fmol/punch, consistent with 7 doses per week or near perfect dosing) to TFV-DP at week 12 and week 48, compared to those not highly adherent at week 12 and 48

Table 1: Studies presented at AIDS 2018 Amsterdam containing evidence on risk compensation

References

1. World Health Organisation, *Guidelines on When to Start Anti-Retroviral Therapy and on Pre-Exposure Prophylaxis for HIV*. 2015.
2. Grulich, A., et al. *Rapid reduction in HIV diagnoses after targeted PrEP implementation in NSW, Australia*. in *IN: Abstracts of the 25th Conference on Retroviruses and Opportunistic Infections (CROI)*. 2018.
3. Fonner, V.A., et al., *Effectiveness and safety of oral HIV pre-exposure prophylaxis (PrEP) for all populations: A systematic review and meta-analysis.* Aids, 2016. **30**(12): p. 1973-83.
4. Nwokolo, N., et al., *Rapidly declining HIV infection in MSM in central London.* The Lancet HIV, 2017. **4**(11): p. e482-e483.
5. Phillips, R.O., A. Fyhri, and F. Sagberg, *Risk Compensation and Bicycle Helmets.* Risk Analysis, 2011. **31**(8): p. 1187-1195.
6. Wilson, N.L., W. Xiong, and C.L. Mattson, *Is sex like driving? HIV prevention and risk compensation.* Journal of development economics, 2014. **106**: p. 78-91.
7. Holt, M. and D.A. Murphy, *Individual Versus Community-Level Risk Compensation Following Preexposure Prophylaxis of HIV.* Am J Public Health, 2017: p. e1-e4.
8. Freeborn, K. and C.J. Portillo, *Does Pre-exposure prophylaxis (PrEP) for HIV prevention in men who have sex with men (MSM) change risk behavior? A systematic review.* J Clin Nurs, 2017.
9. Traeger, M.W., et al., *Effects of Pre-exposure Prophylaxis for the Prevention of Human Immunodeficiency Virus Infection on Sexual Risk Behavior in Men Who Have Sex With Men: A Systematic Review and Meta-analysis.* Clinical Infectious Diseases, 2018: p. ciy182-ciy182.
10. Holt, M., et al., *Community-level changes in condom use and uptake of HIV pre-exposure prophylaxis by gay and bisexual men in Melbourne and Sydney, Australia: results of repeated behavioural surveillance in 2013–17.* The Lancet HIV, 2018.
11. Eaton, J.W., et al., *Health benefits, costs, and cost-effectiveness of earlier eligibility for adult antiretroviral therapy and expanded treatment coverage: a combined analysis of 12 mathematical models.* The lancet global health, 2013. **2**(1): p. 23-34.
12. Grant, H., et al., When are declines in condom use while using PrEP a concern ? Modelling insights from a Hillbrow , South Africa case study. *Journal of the International AIDS Society*, 2017. Vol. 20, no. 1, pp. 1–8.